Lipodystrophy Increases the Risk of CKD Development in HIV-Positive Patients in Switzerland: The LIPOKID Study

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Abstract: Introduction Antiretroviral therapy has improved the life expectancy of patients living with HIV. However, lipodystrophy syndrome (LD) remains prevalent, affecting mostly patients treated with first-generation antiretroviral drugs. This syndrome is characterized by changes in body fat distribution with or without associated metabolic changes. Here, we studied whether clinically evaluated LD is independently associated with chronic kidney disease (CKD) development (sustained estimated glomerular filtration rate [eGFR] $<$ 60 ml/min per 1.73 m) in HIV-positive patients. Methods We conducted a prospective cohort study (the LIPOKID Study) among all the patients from the Swiss HIV Cohort Study (SHCS) with an eGFR $>$60 ml/min per 1.73 m upon their entry into the cohort with more than 3 months of follow-up from January 2002 to August 2016. Cox regression models were used to estimate the association between LD and CKD development. Results Among the 5384 patients included, 1341 (24.9%) developed LD during the follow-up. The mean follow-up time was 72.3 months (SD ±48.4). In total, 252 patients (4.7%) reached the primary endpoint after a median time of 51.3 months (±SD 39.9 months) from inclusion. A diagnosis of LD significantly increased the risk of an eGFR on univariate analysis (hazard ratio [HR] = 2.72; 95% confidence interval [95% CI] = 2.07-3.58; $<$ 0.001) and remained significantly higher after adjustment for known HIV and non-HIV risk factors for CKD (HR = 2.37; 95% CI = 1.67-3.36; $<$ 0.001). The effect of LD on CKD was not mediated through the use of nephrotoxic antiretroviral drugs. Conclusion Lipodystrophy syndrome is independently associated with CKD after adjustment for previously reported risk factors.

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Lipodystrophy Increases the Risk of CKD Development in HIV-Positive Patients in Switzerland: The LIPOKID Study

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Introduction: Antiretroviral therapy has improved the life expectancy of patients living with HIV. However, lipodystrophy syndrome (LD) remains prevalent, affecting mostly patients treated with first-generation antiretroviral drugs. This syndrome is characterized by changes in body fat distribution with or without associated metabolic changes. Here, we studied whether clinically evaluated LD is independently associated with chronic kidney disease (CKD) development (sustained estimated glomerular filtration rate [eGFR] $<$ 60 ml/min per 1.73 m^2) in HIV-positive patients.

Methods: We conducted a prospective cohort study (the LIPOKID Study) among all the patients from the Swiss HIV Cohort Study (SHCS) with an eGFR $>$60 ml/min per 1.73 m^2 upon their entry into the cohort with more than 3 months of follow-up from January 2002 to August 2016. Cox regression models were used to estimate the association between LD and CKD development.

Results: Among the 5384 patients included, 1341 (24.9%) developed LD during the follow-up. The mean follow-up time was 72.3 months (SD ±48.4). In total, 252 patients (4.7%) reached the primary endpoint after a median time of 51.3 months (±SD 39.9 months) from inclusion. A diagnosis of LD significantly increased the risk of an eGFR on univariate analysis (hazard ratio [HR] = 2.72; 95% confidence interval [95% CI] = 2.07−3.58; $P < 0.001$) and remained significantly higher after adjustment for known HIV and non-HIV risk factors for CKD (HR = 2.37; 95% CI = 1.67−3.36; $P < 0.001$). The effect of LD on CKD was not mediated through the use of nephrotoxic antiretroviral drugs.

Conclusion: Lipodystrophy syndrome is independently associated with CKD after adjustment for previously reported risk factors.

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KEYWORDS: albuminuria; chronic kidney disease; HIV; lipids

Chronic kidney disease (CKD) is defined as an alteration in kidney structure and/or function lasting more than 3 months.[1,2] The prevalence of CKD is increasing in the general population and is a major concern for HIV-positive patients,[3] whose life expectancy is reaching that of uninfected patients following the use of combined antiretroviral therapies (ARTs).[4–6] Thus, aging HIV-positive patients are now at risk for metabolic diseases and have a significantly increased risk of developing end-stage renal disease.[7–9] Well-established and HIV-specific risk factors for CKD have been identified in several epidemiological studies. These risk factors include age, diabetes, hypertension, hepatitis B and C co-infections, lower CD4 nadirs, and specific ARTs.[10–14]

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First-generation ARTs are associated with multiple side effects. Lipodystrophy syndrome (LD) was reported in 1998 by Carr *et al*. and is characterized by body shape abnormalities caused by changes in body fat distribution.[15] This syndrome comprises the following 3 phenotypes: lipohypertrophy (LH; fat accumulation mainly in abdominal visceral adipose tissue); lipoatrophy (LA; fat loss in the face, limbs and buttocks); or a mixed pattern of both conditions. The diagnosis of LD is typically made by clinical observation; however, anthropometric evaluations or objective quantification of fat deposition may also be performed.[16] These methods are not used routinely in clinical practice given that they are not widely available, are not well normalized, and do not appear to provide a large benefit compared with that of clinical observation or patient reporting.[15,16] Given the variations in the methods used to diagnose LD, the overall prevalence of the disease among HIV-positive patients ranges from 28% to 60%, depending on the approach used for its diagnosis.[15,17–21] The Swiss HIV Cohort Study (SHCS) reported that although the incidence of LD has decreased with the use of newer molecules in patients who initiated combined ART after 2000,[20] LD remains a prevalent syndrome that has affected 33.9% of the patients in the cohort. The mechanisms underlying LD development in HIV-positive patients are only partially understood. Exposure to specific antiretroviral drugs is likely important in the pathogenesis of LD. However, host and/or viral factors also play an important role in disease development.[22] Clinically, LD is associated with an elevated risk of insulin resistance and dyslipidemia.[23,24] Modifications of adipokine secretion by abnormally deposed fat are associated with these metabolic disturbances in HIV-positive patients.[25]

Evidence suggests that long-term overweight is associated with an increased cumulative risk of CKD in the non-HIV population.[26] Specifically, an elevated waist-to-hip ratio (WHR) in adulthood is associated with a lower measured GFR and lower effective renal plasma flow after multiple adjustments.[26] In addition, in a study of 125 obese patients with type 2 diabetes mellitus, WHR was independently associated with CKD.[27] These observations suggest that central fat distribution, which is often observed in LD, is associated with GFR independently of body mass index (BMI).

Therefore, we hypothesize that LD is independently associated with the development of CKD as defined by an eGFR <60 ml/min per 1.73 m^2. In the LIPOKID Study, we assessed this hypothesis using data prospectively collected in a large nationwide prospective community cohort. We also analyzed the association between LD and albuminuria in a subset of the population.

METHODS

Study Design and Setting

The Swiss HIV Cohort Study (www.shcs.ch) is a nationwide prospective longitudinal cohort collecting clinical and biological data twice a year and involves approximately 75% of all the HIV-positive adults living in Switzerland.[28–30] Data are collected by 5 Swiss university hospitals, 2 tertiary care hospitals, 15 secondary care hospitals, and 36 private physicians. The SHCS is registered on the Swiss National Science longitudinal platform (additional information is available at http://www.shcs.ch).

The SHCS was approved by the ethics committee of each center, and the LIPOKID study was accepted by the scientific board of the SHCS in December 2015. The study findings are reported according to the statement on STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE).[31]

Participants and Eligibility Criteria

All HIV-positive adults who underwent creatinine measurement upon entry into the cohort (baseline) from January 2002 (when routine measurement of serum creatinine began in the SHCS) to August 2016 were included in the primary analysis. Beginning in January 2008, a urine dipstick measurement was performed biannually to semiquantitatively determine whether albuminuria was present. Patients enrolled in this subgroup study from January 2008 to August 2016 were included in the secondary analysis. The following patients were excluded from the study: patients with an eGFR <60 ml/min per 1.73 m^2 at baseline (first visit in the SHCS), patients with no follow-up creatinine measurements, and patients who underwent <3 months of follow-up between the first and last eGFR values. First-semester values for each clinical and biological variable were extracted from the SHCS database for every patient.

Outcomes

The primary outcome was CKD, which was defined as an eGFR <60 ml/min per 1.73 m^2 and confirmed on a second measurement within 6 months. We used a 6-month rather than a 3-month interval to confirm the diagnosis, as patients are seen every 6 months in the SHCS. Therefore, CKD was defined according to the second eGFR measurement. The eGFR was estimated at baseline and at each follow-up visit using the equation for GFR from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[32] We defined eGFR categories based on a CKD stage classification (G1, ≥ 90; G2, 60–89; G3, 30–59; G4, 15–29; and G5, <15 ml/min per 1.73 m^2).[2] Beginning in 2008, dipstick testing was used during the follow-up evaluations of the patients

included in the SHCS, and albuminuria was diagnosed if the dipstick (semiquantitative measure) was positive. The diagnosis was confirmed by a second measurement within 6 months of the original measurement.

Other Variables

The main exposure variable was LD, which was diagnosed based on the results of a routine 6-month questionnaire by the treating physician using clinical judgment (binary variable present/absent). LD is characterized by "fat accumulation" (LH) and/or "fat loss" (LA). LD, LA, and/or LH were considered present in each patient when diagnosed on 2 consecutive visits within a 6-month interval.

Information pertaining to other variables, namely, sociodemographic variables (age, gender, and ethnicity), variables specific for HIV infection (CD4 count, HIV load, hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infection, AIDS status, antiretroviral regimens, and cumulative exposure to ART) and risk factors for cardiovascular and renal diseases (diabetes, high blood pressure, total cholesterol, HDL cholesterol and triglycerides, body mass index, WHR, and smoking status), was also collected. We defined calendar times as follows: 2002 to 2005, 2006 to 2008, and 2009 to 2016.

Study Size

From 2002 to 2016, a total of 6066 patients were included in the SHCS, and 1781 patients (30.7%) were diagnosed with LD during follow-up. We assumed that 25% to 28% of patients with LD would develop CKD, 15% to 18% of patients without LD would develop CKD, and at least 5000 observations would be available. These features provide the study with sufficient power to demonstrate a difference in the incidence of CKD between HIV-infected patients with and without LD.

Statistical Methods

Continuous variables are presented as the mean ± SD, median, and interquartile range, and categorical variables are presented as a frequency and relative percentage. Incidence rates are provided with their 95% confidence intervals (95% CIs). We compared the proportions of eGFR categories by LD phenotypes at baseline and at the last follow-up visit using the χ^2 test. We compared all the descriptive variables between patients included in final analyses and those who were excluded using either the χ^2 test or Student t test, depending on the types of variables.

To explore the association between LD and the primary outcome (an eGFR <60 ml/min per 1.73 m^2), we used a Cox proportional hazards model. First, we assessed multicollinearity among the risk factors at baseline (among diabetes, hypertension, total cholesterol, HDL cholesterol, and triglycerides; among WHR, BMI, total cholesterol, HDL cholesterol, and triglycerides) (*collin* command in Stata). Then we built our multivariate model using a manual forward procedure by starting with the main predictor, LD (binary or in categories), antiretroviral regimens (antiretroviral exposure defined by 2 categories: tenofovir and/or protease inhibitor-based regimen (TDF/PI), and other combinations), and cumulative exposure to TDF and/or PI (<1 year, 12 years, 2−3 years and ≥ 3 years). Then, we introduced each covariate one by one to assess their potential confounding effects on our main association between LD and eGFR <60 ml/min per 1.73 m^2. We also included demographic variables, HIV-related variables, such as current CD4 counts (<199, 200−349, and $\geq 350/mm^3$), HIV load (<1000 copies/ml or ≥ 1000 copies/ml), and the presence of prior AIDS disease, hepatitis B virus seropositivity, and hepatitis C seropositivity. We also tested whether an interaction existed between TDF/PI and cumulative exposure to ART in the multivariable model. Finally, we included established risk factors for renal impairment, such as hypertension, diabetes, dyslipidemia (defined as total cholesterol ≥ 6.2 mmol/l and/or HDL <0.9 mmol/l, and/or triglycerides ≥ 2.26 mmol/l), age in years (as a continuous variable), and baseline eGFR (as a continuous variable). We included the WHR adjusted for gender (introduced as a categorical variable below or above the limit ≥ 0.85 in men and ≥ 0.90 in women). For continuous variables, we verified whether they had a log-linear hazard. All the covariates were introduced as time varying, except for ethnicity and gender. Time included baseline to the first occurrence of CKD.

To test whether the association between LD and CKD was mediated by increased use of TDF, we assessed the combined effect of LD and TDF-based regimens (TDF/PI use) on the risk of CKD. Accordingly, interaction effects were identified on the additive and multiplicative scales. Regarding the additive interaction, the relative excess risk due to interaction was calculated.[33] Finally, we restricted the analysis to the patients who were never treated with TDF/PI during the follow-up, and we reassessed the association between LD and CKD in univariate and multivariate models. For the secondary outcome (albuminuria), we built our multivariate model using the same approach and adjusted for the center to account for some variations in albuminuria measurement methods among the centers. Testing for non-proportional hazards using the Schoenfeld residuals was performed in the final multivariate models.[34]

Sensitivity Analysis

We performed several sensitivity analyses. We defined an eGFR <60 ml/min based on the CKD-EPI equation

without the race factor. We also assessed the composite outcome of eGFR <60 ml/min per 1.73 m^2 and/or albuminuria using the same approach as that for primary and secondary outcomes.

Statistical analyses were performed using STATA IC 15•0 (Stata Statistical Software, Release 14.0; Stata Corporation, College Station, TX).

RESULTS

Participants

Among the 6051 eligible participants from the SHCS, 350 (5.8%) did not have creatinine measurements at entry. In addition, 108 (1.8%) had an eGFR <60 ml/min per 1.73 m^2 at baseline and were thus not included in the statistical analysis. We assessed the risk of renal dysfunction among the 5593 patients who met the eligibility criteria. Of these patients, 209 had no data pertaining to their LD status; thus, a total of 5,384 patients were included in the statistical analysis (Figure 1). Patients who were excluded from the statistical analysis were older (41.3 ± 12.5 years vs. 38.8 ± 10.7 years, $P < 0.001$) and were more often receiving ART (285 [42.7%] vs. 2735 [50.8%], $P < 0.001$), particularly at baseline (235 [35.2%] vs. 1515 [28.1%], $P < 0.001$) than were patients included in the statistical analysis.

Patient Characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of the patients overall, and characteristics between the patients who developed CKD versus those who did not. The patient population included in the study comprised mostly white participants (72.6%) and mostly males (73.7%), with a mean age of 38.8 years. No patients with LD were reported at baseline (i.e., the time of entry into the cohort irrespective of previous ART administration). The mean eGFR at baseline was 106 ml/min per 1.73 m^2. Overall, 79.5% of patients had an eGFR >90 ml/min per 1.73 m^2, and 20.5% had an eGFR between 60 and 90 ml/min per 1.73 m^2. At baseline, 4282 patients (79.5%) were in the G1 eGFR category, and 1102 patients (20.5%) were in the G2 eGFR category (Supplementary Table S1). No patient presented with LD at entry into the study.

The mean number of visits in the SHCS was 17.9 (±14.8), and the mean follow-up time was 72.3 months (SD ±48.4 months). Of the 5384 patients enrolled in the study, 252 (4.7%) reached the primary endpoint.

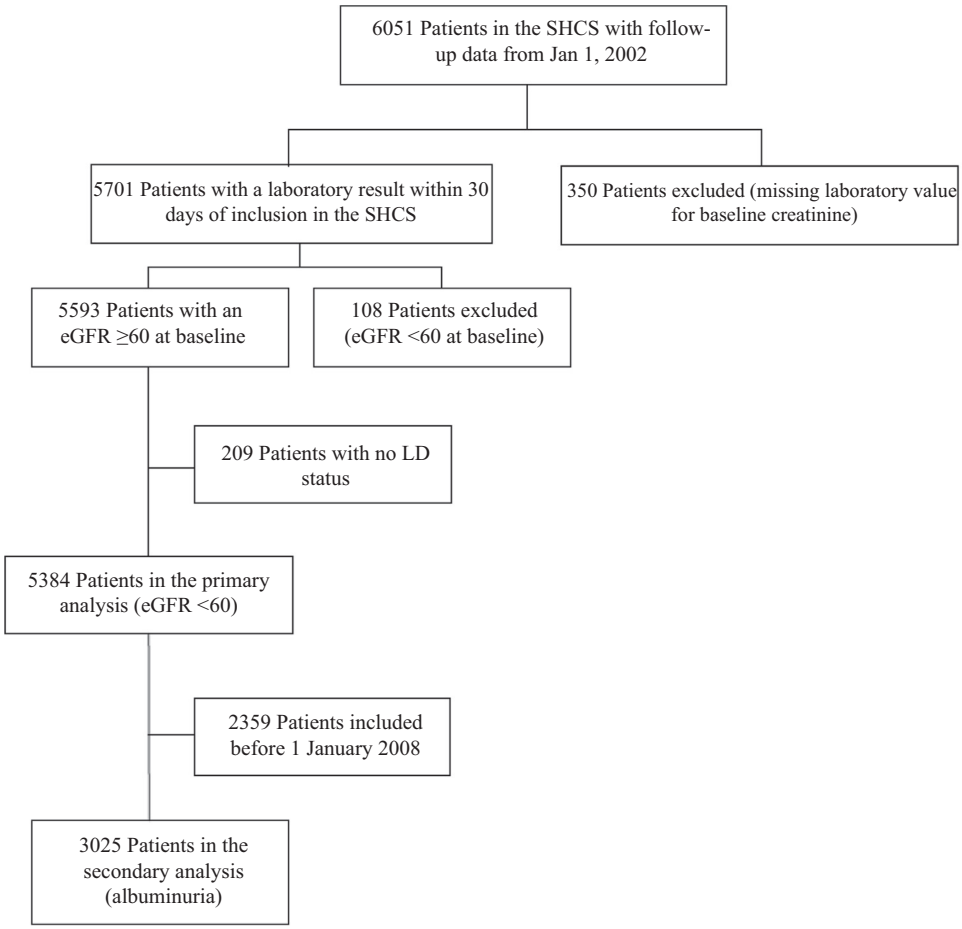

Figure 1. Patient inclusion flow chart. eGFR, estimated glomerular filtration rate; LD, lipodystrophy syndrome; SHCS, Swiss HIV Cohort Study.

Table 1. Demographic and clinical characteristics at baseline

Variables	n = 5384	n = 252 Patients with CKD	n = 5132 Patients Without CKD	*P* value
Socio-demographic				
Mean age, yr (±SD, median, min–max)	38.8 (±10.7, 38, 16–80)	51.0 (±12.7, 50.5, 19–80)	38.2 (±10.2, 37, 16–79)	<0.001
Gender, n (%)				0.595
Men	3966 (73.7)	182 (72.2)	3784 (73.7)	
Women	1418 (26.3)	70 (27.8)	1348 (26.3)	
Ethnicity, n (%)				<0.001
White	3906 (72.6)	224 (88.9)	3682 (71.8)	
Black	942 (17.5)	11 (4.4)	931 (18.2)	
Hispano-American	252 (4.7)	5 (2.0)	247 (4.8)	
Asian	269 (5.0)	11 (4.4)	258 (5.0)	
Other	11 (0.2)	1 (0.4)	9 (0.2)	
HIV infection				
Mean initial CD4 count (±SD, median, min–max)	388 (±271, 355, 1–2851)	335 (±265, 280, 3–1421)	391 (±271, 358, 0–2851)	0.0014
Categories of CD4 count, cells/μl (%)				0.003
<200	1413 (26.2)	89 (35.3)	1324 (25.8)	
200–349	1231 (22.9)	61 (24.2)	1170 (22.8)	
350–499	1200 (22.3)	43 (17.1)	1157 (22.5)	
≥500	1540 (28.6)	59 (23.4)	1481 (28.9)	
Mean initial RNA count, $\log_{10}$ (±SD, median, min–max)	4.1 (±1.3, 4.3, 0.3–8.7)	4.1 (±1.5, 4.2, 0.8–8.1)	4.0 (±1.3, 4.3, 0.3–8.7)	0.863
Categories of RNA, n (%)				0.095
<80	533 (9.9)	21 (8.4)	512 (10.0)	
80–1999	459 (8.6)	17 (6.8)	442 (8.6)	
2000–9999	650 (12.1)	21 (8.4)	629 (12.3)	
≥10,000	3728 (69.4)	191 (76.4)	3537 (69.1)	
Route of HIV transmission, n (%)				0.070
MSM	2563 (47.6)	102 (40.5)	2461 (48.0)	
Heterosexual	2104 (39.1)	109 (43.2)	1995 (38.9)	
IDU	431 (8.0)	28 (11.1)	403 (7.9)	
Blood products	35 (0.7)	3 (1.2)	32 (0.6)	
Perinatal transmission	62 (1.2)	0 (0)	62 (1.2)	
Unknown	144 (2.7)	8 (3.2)	136 (2.6)	
Other	45 (0.8)	2 (0.8)	43 (0.8)	
AIDS status, n (%)	736 (13.7)	55 (21.8)	681 (13.3)	<0.001
Co-infection with HBV, n (%)	1673 (31.1)	96 (38.1)	1577 (30.7)	0.014
Co-infection with HCV, n (%)	427 (7.9)	18 (7.1)	409 (8.0)	0.635
No ART at baseline, n (%)	2739 (50.9)	118 (46.8)	2621 (51.1)	0.188
ART drugs used among patients treated, n (%)				
Tenofovir	1515 (28.1)	71 (28.2)	1444 (28.1)	0.990
Ritonavir	1159 (21.5)	66 (26.2)	1093 (21.3)	0.065
Cardiovascular and other risk factors				
Family history of cardiovascular disease, n (%) (n = 5367)	540 (10.1)	25 (9.9)	515 (10.1)	0.994
Family history of diabetes, n (%) (n = 2790)	501 (18.0)	21 (26.9)	480 (17.7)	0.112
Personal history of diabetes, n (%)	177 (3.3)	29 (11.5)	148 (2.9)	<0.001
Personal history of high blood pressure, n (%) (n = 5357)	329 (6.1)	47 (18.7)	282 (5.5)	<0.001
Smoking habits, n (%) (n = 5284)	2279 (43.1)	85 (34.8)	2194 (43.5)	0.007
i.v. Heroin use, n (%) (n = 3369)	45 (1.3)	1 (0.9)	44 (1.4)	0.875
i.v. Cocaine use, n (%) (n = 3369)	78 (2.3)	2 (1.8)	76 (2.3)	0.888
Cannabis consumer, n (%) (n = 3368)	590 (17.5)	13 (11.7)	577 (17.7)	0.215
LD, n (%) (n = 5384)				
No LD	5384 (100)	252 (100)	5132 (100)	—
Mean creatinine, μmol/l (±SD, median, min–max)	76.1 (±15.8, 76, 11–135)	86.4 (±16.1, 86, 35–131)	75.6 (±15.6, 76, 11–135)	<0.001
Mean GFR, ml/min per 1.73 m^2 (±SD, median, min–max)	106 (±19.3, 106, 60.2–238.4)	84.7 (±18.0, 80.9, 60.3–171)	107.1 (±18.7, 107, 60.2–238.4)	<0.001
GFR stages, n (%)				<0.001
G1	4282 (79.5)	86 (34.1)	4196 (81.8)	
G2	1102 (20.5)	166 (65.9)	936 (18.2)	
Albuminuria, n (%)	85 (1.6)	4 (1.6)	81 (1.6)	0.991
Mean weight, kg (±SD, median, min–max) (n = 4670)	71.1 (±13.6, 70, 35–197)	70.7 (±13.2, 71, 42–116)	71.2 (±13.6, 70, 35–197)	0.6475
Mean BMI, kg/m^2 (±SD, median, min–max) (n = 4670)	23.6 (±3.8, 23.1, 14.3–74.0)	23.9 (±3.8, 23.5, 16.7–41.0)	23.6 (±3.8, 23.1, 14.3–74)	0.2281

(Continued on next page)

Table 1. (Continued)

Variables	n = 5384	n = 252 Patients with CKD	n = 5132 Patients Without CKD	*P* value
BMI categories, n (%) (n = 4670)				0.480
BMI <18.5 kg/m^2	267 (5.7)	12 (5.7)	255 (5.7)	
18.5–25	3003 (64.3)	125 (59.5)	2878 (64.5)	
25–30	1125 (24.1)	59 (28.1)	1066 (23.9)	
≥30	275 (5.9)	14 (6.7)	261 (5.9)	
Mean cholesterol, mmol/l (±SD, median, min–max) (n = 4988)	4.55 (±1.13, 4.45, 1.50–13.80)	4.78 (±1.23, 4.60, 2.40–10.8)	4.53 (±1.12, 4.42, 1.50–13.80)	0.0015
Mean HDL, mmol/l (±SD, median, min–max) (n = 4647)	1.17 (±0.44, 1.1, 0.02–5.6)	1.08 (±0.41, 1.03, 0.19–3.13)	1.17 (±0.44, 1.10, 0.02–5.60)	0.0031
Mean cholesterol/HDL ratio (±SD, median, min–max) (n = 4641)	4.37 (±2.41, 4.0, 0.70–80.0)	4.87 (±1.74, 4.62, 1.75–13.53)	4.35 (±2.44, 3.99, 0.70–80.0)	0.0016
Mean triglycerides, mmol/l (±SD, median, min–max) (n = 4976)	1.73 (±1.31, 1.40, 0.02–26.74)	2.17 (±1.48, 1.85, 0.40–10.83)	1.71 (±1.29, 1.37, 0.02–26.74)	<0.001
Mean hip values, cm (±SD, median, min–max) (n = 4782)	94.6 (±9.3, 94, 10–170)	95.5 (±8.9, 95, 67–136)	94.5 (±9.34, 94, 10–170)	0.1354
Mean waist values, cm (±SD, median, min–max) (n = 4790)	84.5 (±11.0, 84, 55–172)	87.1 (±11.2, 87, 64–133)	84.4 (±11.0, 83, 55–172)	0.0003
Mean waist–hip ratio (±SD, median, min–max) (n = 4781)	0.90 (±0.17, 0.89, 0.58–11.7)	0.91 (±0.07, 0.91, 0.76–1.11)	0.89 (±0.18, 0.89, 0.58–11.7)	0.1449
In men (n = 3573)	0.91 (±0.19, 0.90, 0.63–11.7)	0.93 (±0.07, 0.93, 0.78–1.11)	0.91 (±0.20, 0.90, 0.63–11.7)	0.1622
In women (n = 1208)	0.85 (±0.08, 0.85, 0.58–1.45)	0.86 (±0.06, 0.85, 0.76–1.02)	0.85 (±0.08. 0.85, 0.58–1.45)	0.2713

ART, antiretroviral therapy; BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; IDU, intravenous drug user; LD, lipodystrophy syndrome; MSM, men having sex with men.

Of the 5384 patients with data pertaining to their LD status, 1341 (24.9%) were reported to have LD on 2 consecutive visits and at least once during the follow-up period. The overall incidence of LD was 53.0 per 1000 patient-years (95% CI = 50.2−55.9). It was 68.3 (95% CI = 59.8−78.1) in 2002 to 2005, 30.2 (95% CI = 27.0−33.8) in 2006 to 2008, and 34.3 per 1000 patient-years (95% CI = 32.0−36.7) in 2009 to 2016. Overall, 912 patients (16.9%) developed LH, 327 (6.1%) patients developed LA, and 102 (1.9%) developed both LA and LH. Of these patients, 1314 (98.0%) were treated with ARTs for a mean time of 34.2 months (±SD 39.2 months) until the first report of LD. The mean time from the first LD report to the primary endpoint was 51.3 months (±SD 39.9, median = 40.4, interquartile range = 17.6−81.7 months). Twenty-two patients (1.6%) reported the occurrence of LD after the development of the primary outcome and were therefore not included in the survival analysis

Association Between Lipodystrophy and an eGFR <60 ml/min per 1.73 m^2

Per the univariate analysis (Table 2), LD exhibited a significantly increased hazard ratio (HR) of 2.7 for the development of CKD (Figure 2). The combination of LA+LH was associated with a significantly increased HR of 3.5 for development of CKD. Fat loss alone was associated with a significantly increased HR of 3.0, and LH alone was associated with a significantly increased HR of 2.6. The presence of LD was significantly associated with an increased HR of 2.4 for the development of CKD via multivariable analysis after adjustment for known CKD risk factors and prespecified confounders (Table 2). A significant interaction was observed between the TDF/PI-based regimen and cumulative exposure: longer exposure to a TDF/PI-based regimen corresponded to a higher risk of CKD. The LD phenotypes were also significantly associated with an increased HR for CKD development (Supplementary Table S2). Compared with no LD, LA alone exhibited an increased HR of 2.3, LH alone exhibited an increased HR of 2.1, and the combination of LA and LH exhibited an increased HR of 2.8. Other independent risk factors for developing CKD were low baseline eGFR, older age, low HIV load, exposure to TDF/PI regimens, cumulative exposure to ART, co-infection with HBV, diabetes, and nonblack ethnicity.

In the sensitivity analysis, we confirmed that LD was associated with an increased risk of CKD (HR = 2.39, 95% CI = 1.70−3.36, $P < 0.001$ with CKD-EPI without the race factor. The nonblack ethnicity risk was no longer significant in this analysis.

Regarding the interaction analysis between LD and TDF/PI use, no evidence was observed for a multiplicative interaction between LD and TDF/PI use (HR = 1.43, $P = 0.295$). For the additive interaction, the relative excess risk due to interaction was positive and significant, suggesting that the combination of 2 hazards was larger than the sum of the number of events that would be associated with the individual risk factors separately (relative excess risk due to interaction = 3.18, 95% CI = 0.19−6.18, $P = 0.0372$). In the model restricted to patients who had never received TDF/PI during their follow-up (n = 3196), we confirmed that LD was associated with an increased hazard of CKD in the univariate model (HR = 2.90, 95% CI = 1.86−4.52,

Table 2. Univariate (left) and multivariable (right) associations between CKD (which is defined as an eGFR <60 ml/min per 1.73 m^2) and LD and known risk factors for CKD

	Univariate analysis	Multivariable analysis
Variables	**Hazard ratio (95% CI), *P* value**	**Hazard ratio (95% CI), *P* value**
Category of lipodystrophy (reference no LD)	**$P < 0.001$**	—
Fat loss (LA)	**2.96 (1.89–4.64), $P < 0.001$**	
Fat accumulation (LH)	**2.57 (1.88–3.52), $P < 0.001$**	
Fat loss and accumulation (LH + LA)	**3.47 (1.62–7.44), $P = 0.001$**	
Lipodystrophy (reference, no LD)	**2.72 (2.07–3.58), $P < 0.001$**	**2.37 (1.67–3.36), $P < 0.001$**
Baseline GFR, ml/min per 1.73 m^2	**0.93 (0.92–0.94), $P < 0.001$**	**0.95 (0.93–0.96), $P < 0.001$**
HIV-associated risk factors for renal outcomes		
AIDS status at baseline	**1.87 (1.39–2.52), $P < 0.001$**	0.96 (0.66–1.38), $P = 0.817$
HIV infection route (reference, heterosexuals)	**$P = 0.001$**	—
IDU	**1.58 (1.04–2.39), $P = 0.031$**	
Men having sex with men	**0.71 (0.55–0.94), $P = 0.015$**	
Other	**0.83 (0.47–1.48), $P = 0.536$**	
CD4 count during follow-up (reference, CD4 ≥350/mm^3)	**$P = 0.017$**	$P = 0.473$
200–349	**1.40 (1.01–1.94), $P = 0.041$**	1.22 (0.82–1.82), $P = 0.320$
<199	**1.63 (1.09–2.44), $P = 0.017$**	0.86 (0.46–1.61), $P = 0.642$
Viremia ≥1000 copies/ml (reference, <1000)	**0.35 (0.23–0.53), $P < 0.001$**	**0.30 (0.17–0.53), $P < 0.001$**
Tenofovir and/or protease inhibitor–based regimen (reference, other)	**2.07 (1.60–2.67), $P < 0.001$**	—
Cumulative exposure to ART (reference, ≥3 year)	$P = 0.112$	—
<1 year	1.51 (1.02–2.24), $P = 0.042$	
1–2 years	0.94 (0.56–1.56), $P = 0.801$	
2–3 years	1.30 (0.93–1.83), $P = 0.129$	
Interaction between TDF/PI-based regimen and cumulative exposure to ART	P = 0.328	$P = 0.021$
TDF/PI-based regimen and <1 year (ref. other ART)	**2.50 (1.43–4.39), $P = 0.001$**	1.39 (0.84–2.31), $P = 0.203$
TDF/PI-based regimen and 1–2 years	2.25 (0.96–5.31), $P = 0.063$	1.36 (0.99–1.85), $P = 0.055$
TDF/PI-based regimen and 2–3 years	**1.65 (1.12–2.42), $P = 0.011$**	**3.80 (1.46–9.92), $P = 0.006$**
TDF/PI-based regimen and ≥3 years	**2.98 (1.71–5.19), $P < 0.001$**	**3.33 (1.79–6.22), $P < 0.001$**
HBV co-infection (reference, no co-infection)	**1.62 (1.27–2.08), $P < 0.001$**	**1.63 (1.19–2.23), $P = 0.002$**
HCV co-infection (reference, no co-infection)	**1.55 (1.08–2.23), $P = 0.017$**	1.38 (0.87–2.20), $P = 0.167$
Other risk factors associated with the primary outcome		
Male gender	0.91 (0.69–1.20), $P = 0.491$	0.80 (0.51–1.25), $P = 0.324$
Age, yr (continuous variable)	**1.10 (1.08–1.11), $P < 0.001$**	**1.06 (1.04–1.08), $P < 0.001$**
Diabetes (reference, no diabetes)	**4.12 (2.73–6.23), $P < 0.001$**	**1.86 (1.12–3.10), $P = 0.017$**
Hypertension (reference, no hypertension)	1.30 (0.80–2.13), $P = 0.294$	0.92 (0.55–1.56), $P = 0.765$
Nonblack ethnicity (reference, black ethnicity)	**4.53 (2.48–8.30), $P < 0.001$**	**5.04 (1.79–14.19), $P = 0.002$**
BMI (reference BMI <18.5 kg/m^2)	**0.025**	—
18.5–25	**1.75 (1.00–3.05), $P = 0.050$**	
25–30	**1.41 (1.06–1.89), $P = 0.020$**	
≥30	**1.56 (1.02–2.38), $P = 0.040$**	
Waist–hip ratio adjusted for gender above the limit (reference <0.85 in men and <0.90 in women)	1.25 (0.93–1.67), $P = 0.138$	0.71 (0.44–1.14), $P = 0.155$
Dyslipidemia (reference, no dyslipidemia)	**1.81 (1.35–2.43), $P < 0.001$**	
Smoker (reference, no smoking)	**0.75 (0.58–0.98), $P = 0.032$**	0.84 (0.60–1.18), $P = 0.312$

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; PI, protease inhibitors; ref., reference; TDF, tenofovir.
Boldface type denotes results with a *P* value of <0.05.

$P < 0.001$). The association between LD and CKD remained significant after adjustment for other risk factors (HR = 1.91, 95% CI = 1.07−3.39, $P = 0.028$).

Association Between LD and Albuminuria in Patients Included in the Cohort After 2008

A total of 2359 patients (43.8%) were enrolled in the SHCS before 1 January 2008, the date after which proteinuria dipstick testing was systematically performed, and thus were excluded from the subgroup analysis regarding albuminuria (Figure 1). Among the patients enrolled in the subgroup (n = 3,025), 555 (18.3%) developed LD during follow-up. Albuminuria occurred after a mean time of 17.1 months (±14.3, median time = 16.5, interquartile range = 4.8−22.9 months). A total of 44 patients were first diagnosed with LD after developing albuminuria and were thus not included in the survival analysis. To account for some differences among the centers regarding albuminuria measurement by dipstick, we adjusted secondary analyses for centers. Univariate analyses are presented in Table 3. LD was not significantly

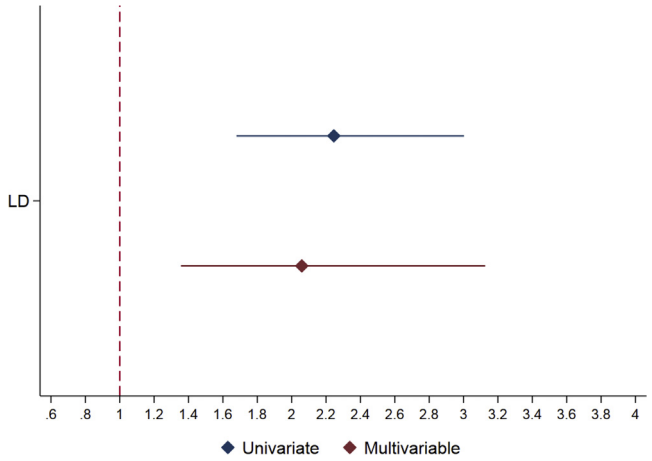

Figure 2. Forest plot of chronic kidney disease (CKD) by lipodystrophy syndrome (LD) in univariate and multivariable models.

associated with albuminuria on univariate analysis. The association between LD and albuminuria remained nonsignificant after adjustment for the main CKD risk factors (Supplementary Table S3). In the sensitivity analysis, we confirmed that LD was not significantly associated with the composite outcome (HR = 1.17, 95% CI = 0.84−1.63, $P = 0.362$) after adjustment for the main risk factors.

CONCLUSION

In this large prospective nationwide cohort including HIV-positive patients in Switzerland, we observed that LD was associated with the development of CKD (defined as an eGFR <60 ml/min per 1.73 m^2), independent of classic and HIV-associated CKD risk factors such as diabetes, hypertension, cumulative exposure to a TDF/PI-based regimen or viral load, as well as lipid metabolism alterations and WHR modifications. Age, co-infection with hepatitis B, and exposure to a TDF/PI-based regimen were also independently associated with an increased hazard ratio for an eGFR <60 ml/min per 1.73 m^2. We did not identify an association between LD and albuminuria. The association with LD was not mediated through increased use of TDF (with or without PI), as demonstrated in the multivariable analysis.

This is the first study with a long follow-up and a large, well-followed cohort to report an association between clinically defined LD and the later development of CKD in HIV-positive patients. Metabolic and common risk factors could not explain our observation, and the independent risk conferred by LD is high. This observation is of great clinical importance, as a large fraction of HIV patients display the LD phenotype. Therefore, our observations imply that specific kidney surveillance should be performed in this population, and that nephrotoxic drugs, including ARTs, should

Table 3. Univariate associations between LD and albuminuria and known risk factors for CKD

Variables	Hazard ratio (95% CI), *P* value
Categories of lipodystrophy (reference, no LD)	$P = 0.366$
Fat loss (LA)	0.99 (0.67–1.50), $P = 0.99$
Fat accumulation (LH)	1.64 (0.94–2.88), $P = 0.081$
Fat loss and accumulation (LH + LA)	0.74 (0.10–5.26), $P = 0.760$
Lipodystrophy (reference, no LD)	1.13 (0.81–1.59), $P = 0.464$
HIV-associated risk factors for renal outcomes	
AIDS status at baseline	**1.48 (1.12–1.96), $P = 0.006$**
HIV infection route (reference, heterosexuals)	$P = 0.161$
IDU	1.20 (0.94–1.54), $P = 0.140$
Male–male intercourse	**1.62 (1.03–2.56), $P = 0.037$**
Other	1.08 (0.66–1.79), $P = 0.757$
CD4 count during follow-up (reference, CD4 ≥350/mm^3)	**$P < 0.001$**
200–349	**1.52 (1.16–1.99), $P = 0.002$**
<199	**1.75 (1.25–2.43), $P = 0.001$**
Log_{10} viremia during follow-up	**0.73 (0.57–0.94), $P = 0.015$**
Exposure to a TDF/PI-based regimen (reference, other)	**1.61 (1.39–1.88), $P < 0.001$**
HBV co-infection (reference, no co-infection)	**1.45 (1.16–1.81), $P = 0.001$**
HCV co-infection (reference, no co-infection)	1.35 (0.92–1.99), $P = 0.129$
Other risk factors associated with the primary outcome	
Age	**1.02 (1.01–1.03), $P < 0.001$**
Diabetes (reference, no diabetes)	**1.86 (1.07–3.24), $P = 0.029$**
Hypertension (reference, no hypertension)	**2.11 (1.47–3.03), $P < 0.001$**
Nonblack ethnicity (reference, black ethnicity)	0.92 (0.68–1.25), $P = 0.595$
BMI	0.99 (0.96–1.02), $P = 0.394$
Waist–hip ratio above limit[a]	**1.55 (1.18–2.05), $P = 0.002$**
Total cholesterol	**1.11 (1.01–1.21), $P = 0.030$**
HDL cholesterol	0.76 (0.58–1.00), $P = 0.054$
Triglycerides	1.02 (0.99–1.05), $P = 0.227$
Smoking habits	**1.28 (1.03–1.59), $P = 0.023$**

BMI, body mass index (continuous time-dependent variable); CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; NRTI, nucleoside reverse transcriptase inhibitors; RTV, ritonavir; TDF, tenofovir.
Boldface type denotes results with a *P* value of <0.05.
[a]Adjusted for gender.

generally be administered with caution in these patients, as the risks of CKD may be additive.

Some hypotheses may explain how LD may be associated with the development of CKD independent of other factors. Adipokines modulate kidney lesions and fibrosis progression.[35,36] A human case-control study revealed an association between alterations in specific adipokines and the presence of CKD.[37] Therefore, the modification of adipokines, which is known to occur in LD,[25,38] may underlie the observed association between LD and the incidence of CKD.

Our study results contrast with those of the study by Malkina et al.,[39] who did not observe statistically significant associations between magnetic resonance imaging−measured regional adiposity or serum adipokines and rapid kidney functional decline or incidental CKD. However, the number of patients and the average follow-up period of 5 years were likely too small and too brief, respectively, to observe differences in

outcomes, as we demonstrated that the development of an eGFR <60 ml/min occurred after a mean observation time of 6 years.

In the present study, the association between LD and kidney disease was restricted to eGFR and did not affect albuminuria, which may be explained by the low number of patients available with albuminuria measurements, the low sensitivity of dipstick testing, or the shorter follow-up in this subgroup of patients. Also, the incidence of LD was drastically reduced in 2008 in patients with albuminuria data, which can be explained by the fact that drugs associated with LD such as zidovudine, stavudine, and protease inhibitors were less prescribed from 2008. Alternatively, LD may induce CKD by nonglomerular lesions and may therefore be independent of albuminuria.

Some additional observations warrant commentary. A clear association between combined ART, including TDF alone or in combination with a PI, and the development of an eGFR <60 ml/min per 1.73 m^2 was identified by multivariable analysis in a cumulative fashion. This association was previously reported in a case-control study with TDF in combination with a ritonavir boost, resulting in greater renal function decline over 48 weeks, and may rely on a drug−drug interaction between ritonavir and TDF.[40] No association was identified between an eGFR <60 ml/min per 1.73 m^2 and diabetes or hypertension. These findings may be explained by the relatively young mean age of the patients in this cohort and thus the relatively short follow-up period of the study. Nonetheless, we found that diabetes and hypertension were both independently associated with an increased HR for albuminuria. In addition, the low baseline prevalence of AIDS (13.7%) and early HIV diagnoses may explain the surprising observation that the risk of CKD was decreased in patients with a high viral load compared with those with a low viral load. AIDS status did not seem to be a risk factor for an eGFR <60 ml/min per 1.73 m^2 but was strongly associated with the development of albuminuria, a key feature of HIV-associated nephropathy.[41]

We also observed an association between an eGFR <60 ml/min per 1.73 m^2 and ethnicity, as patients of sub-Saharan descent had a reduced HR for the development of CKD compared with other groups. This was likely related to the use of the race factor for eGFR estimation, as this association was not significant in a sensitivity analysis excluding its use and adjusting for age in the equation. Indeed, eGFR formulas corrected for ethnicity may overestimate the renal function in African Europeans.[42]

Our study had some limitations. First, our findings are based on observational data, which may weaken the assessment of causal relationships between risk factors and outcome. Therefore, the study cannot distinguish between LD itself or a risk factor for LD (e.g., long-term use of early nucleoside reverse transcriptase inhibitors) as the causal link to CKD. However, our aim was to determine whether the presence of clinical LD should lead to a higher suspicion of CKD independent of factors that causally link the 2 events. In addition, LD was diagnosed clinically, as currently recommended, rather than by body composition measurements, given that radiologic methods are not well standardized and are cumbersome to perform at the population level. Although the definition of LD used herein is not standardized, it is similar to that used in routine clinical practice. Clinician assessment exhibits substantial agreement with a more comprehensive assessment of LD ($\kappa = 0.65$; $P < 0.001$) and has been used previously in several studies.[20,43] To decrease the risk of misclassification with respect to the diagnosis of LD, we diagnosed LD only in patients with 2 consecutive LD diagnoses within a 6-month period.

Second, albuminuria was measured by dipstick testing, and the coding for the diagnosis of this semi-quantitative variable (−, +, ++, and +++) may have prevented a standardization among the 7 SHCS centers. In addition, GFR was estimated using the CKD-EPI formula derived from creatinine. This equation is used to estimate renal function in patients with HIV.[44] However, the accuracy of the CKD-EPI formula is still lower than that used for other populations.

In conclusion, to our knowledge this is the first report demonstrating that clinically diagnosed LD is associated with CKD independently of known risk factors in a large prospective nationwide cohort study. Our findings suggest that HIV-positive patients with LD should be monitored more closely with respect to renal function. In addition, exposure to nephrotoxic ARTs (e.g., TDF) should be minimized in these patients. Additional works exploring the pathophysiology of this clear association are needed.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

YB, SDS, and AC designed the study; AGA, YB, EB, CF, SDS, and AC analyzed the data; AGA performed the statistical analysis; MB, MH, CS, LM, and HK reviewed the manuscript; YB, SDS, AGA, and AC wrote the manuscript.

SUPPLEMENTARY MATERIAL

Table S1. Distribution of GFR stage at baseline and the last follow-up visit based on the presence of LD. [1]Comparison of GFR category proportions between patients with and without LD at the last follow-up visit (chi-squared test 20.1, $P < 0.001$). [2]Comparison of GFR category proportions among LD phenotypes at the last follow-up visit (chi-squared test 49.8, $P < 0.001$).

Table S2. Alternative multivariable model for the development of an eGFR <60 ml/min per 1.73 m^2. AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CI, confidence interval; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; LA, lipoatrophy; LD, lipodystrophy; LH, lipohypertrophy; NRTI, nucleoside reverse transcriptase inhibitors; RTV, ritonavir; TDF, tenofovir. Model adjusted for the variables mentioned. In bold: $P < 0.05$.

Table S3. Multivariable models for the development of albuminuria. The model was also adjusted for the center (global P value <0.001). AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CI, confidence interval; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; LA, lipoatrophy; LD, lipodystrophy; LH, lipohypertrophy; NRTI, nucleoside reverse transcriptase inhibitors; RTV, ritonavir; TDF, tenofovir. In bold: $P < 0.05$.

Appendix S1. Members of the Swiss HIV Cohort Study group.

Supplementary information linked to the online version of the paper at www.kireports.org.

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